

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 33-36 are pending after entry of the amendments set forth herein.

Claims 1-32 are canceled without prejudice.

Please replace claims 33-36 with the clean version provided above.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Amendment to the Specification

The specification is amended to provide a correct cross-reference to related applications.

Amendment to the Claims

New claims 33-36 are added.

The specification of the instant application describes that, since RNA is typically short-lived and unstable, a cDNA library is produced from RNA in a biological sample (*see* page 10, lines 4 through page 12, line 16). The abundance of cDNA sequences in a library represents the abundance of RNA in the original biological sample (*see* page 33, line 20 through page 34, line 11).

Exemplary, specific support in the specification for each of new claims 33-36 is detailed in the tables below:

Atty Dkt. No.: 06514069CON
 USSN: 09/956,999

<p>Element of New Claim 33</p>	<p>Support in Specification</p>
<p>A method for disease diagnosis, comprising the steps of:</p>	<p>Page 6, lines 3-4 and 9-10; page 29, lines 19-20; page 34, lines 2-4; page 40, lines 14-20; page 42, lines 14-17; claims 16, 20, 23, 29, and 32.</p>
<p>comparing a first ratio, obtained from a sample comprising non-diseased cells, of a reference RNA, the expression level of which is not expected to be altered in a diseased cell, to a target RNA, the expression level of which is expected to be altered in a diseased cell, with a second ratio, obtained from a test sample, of said reference RNA to said target RNA; and</p>	<p>Page 29, lines 15-23 (detect differential expression between diseased and non-diseased cells); page 30, lines 14-17 (analyze ratios); page 33, line 20 through page 34, line 11 (differential expression); page 35, lines 7-11 (use normalized abundances to determine ratios of expression); page 42, lines 22 through page 43, line 15 (compare ratios of expression of genes having altered expression levels); page 44, lines 13-22 (compare ratios); page 45, lines 8-17 (compare ratios); claims 14-32.</p>
<p>determining whether there is a statistically-significant difference between said first ratio and said second ratio, the presence of statistically-significant difference being indicative of the presence of diseased cells in said test sample.</p>	<p>Page 35, lines 17-25 (significance value calculation for abundance differences); page 42, lines 20-27 (use differential expression to discriminate between diseased and normal cells).</p>

<p>Element of New Claim 34</p>	<p>Support in Specification</p>
<p>A method for detecting a difference in RNA expression between first and second samples, comprising the steps of comparing a ratio of a first RNA to a second RNA in a first sample with said ratio in a second sample.</p>	<p>Page 30, lines 14-17; page 34, lines 2-4; page 35, lines 7-11; page 42, lines 22 through page 43, line 15; page 44, lines 13-24; page 45, lines 8-19; claims 14-32.</p>

Element of New Claim 35	Support in Specification
A method for identifying a gene, the expression of which is associated with a disease,	Page 9, lines 20-24; page 36, lines 22-26; page 43, lines 18-27; claims 13, 17, 25, and 31.
comprising the steps of comparing a ratio, in a disease sample, of an RNA expression product of said gene to an RNA expression product of a reference gene that is not affected by disease, with said ratio in a non-diseased sample,	Page 29, lines 15-23 (detect differential expression between diseased and non-diseased cells); page 30, lines 14-17 (analyze ratios); page 33, line 20 through page 34, line 11 (differential expression); page 35, lines 7-11 (use normalized abundances to determine ratios of expression); page 42, lines 22 through page 43, line 15 (compare ratios of expression of genes having altered expression levels); page 44, lines 13-22 (compare ratios); page 45, lines 8-19 (compare ratios); claims 14-32.
the presence of a statistically-significant difference between said ratios being indicative of a gene, the expression of which is associated with the disease.	Page 35, lines 17-25 (significance value calculation for abundance differences); page 42, lines 20-27 (use differential expression to discriminate between diseased and normal cells)

Element of New Claim 36	Support in Specification
A method for disease diagnosis, comprising the steps of:	Page 6, lines 3-4 and 9-10; page 29, lines 19-20; page 34, lines 2-4; page 40, lines 14-20; page 42, lines 14-17, claims 20, 26, and 32.
(a) counting molecules of a first RNA, the expression of which is not different in a diseased cell as compared to a non-diseased cell;	Page 29, lines 15-23 (detect differential expression between diseased and non-diseased cells); page 30, lines 14-17 (analyze ratios); page 33, line 20 through page 34, line 11 (differential expression); page 35, lines 7-11 (use normalized abundances to determine ratios of expression); page 42, lines 22 through page 43, line 15 (compare ratios of different genes); page 44, lines 13-22 (compare ratios); page 45, lines 8-19 (compare ratios); claims 14-32.
(b) counting molecules of a second RNA, the expression of which is expected to be different in a diseased cell as compared to a non-diseased cell;	
(c) determining whether a statistically-significant difference exists between numbers of said first RNA and said second RNA, the presence of a statistically-significant difference being indicative of a disease.	Page 35, lines 17-25 (significance value calculation for abundance differences); page 42, lines 20-27 (use differential expression to discriminate between diseased and normal cells).

In accordance with the requirements of 37 CFR §1.607, applicants submit that new claims 33-36 are identical to claims 1-3 and 5, respectively of U.S. Patent No. 6,146,828, issued November 14, 2000. Applicants present new claims 33-36 as proposed counts in an interference with U.S. Patent No. 6,146,828, and submit that claims 1-3 and 5 correspond to the proposed counts.

With the addition of new claims 33-36, the present application claims the same or substantially the same subject matter as claims 1-3, and 5 of US Pat. No. 6,146,828, prior to one year from the November 14, 2000 issue date of US Pat. No. 6,146,828, in accordance with 35 USC §135(b).

No new matter has been added by these amendments or new claims.

Conclusion

In the event that the transmittal letter is separated from this document and the Patent Office determines that extensions or other relief is required and/or fees are due applicants, the Applicant petitions for any required relief, including extensions of time, and authorize the Commissioner to charge our Deposit Account No. 50-0815, Order Number 6514069CON, for any fees due in connection with the filing of this document. The Patent Office is not authorized to charge issue fees to our Deposit Account.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

The first paragraph under the heading "CROSS-REFERENCE TO RELATED APPLICATIONS" on page 1 has been replaced with the following rewritten paragraph:

This application is a continuation of U.S. application number 08/969,987, filed November 13, 1987, now U.S. Patent No. 6,303,297, which [This] application is a continuation-in-part of:

- 1) U.S. application serial no. 08/282,955, filed July 29, 1995, which is a continuation-in-part of U.S. application serial no. 08/187,530, filed January 27, 1994, which is a continuation-in-part of:
 - a) U.S. application serial no. 08/179,873, filed January 11, 1994; and
 - b) U.S. application serial no. 08/100,523, filed August 3, 1993, which is a continuation-in-part of U.S. application serial no. 07/977,780, filed November 19, 1992, which is a continuation-in-part of U.S. application serial no. 07/916,491, filed July 17, 1992;
- 2) U.S. application serial no. 08/289,822, filed August 12, 1994; and
- 3) U.S. application serial nos:
 - a) U.S. application serial no. 08/581,240, filed December 29, 1995;
 - b) U.S. application serial no. 08/657,697, filed May 29, 1996;
 - c) U.S. application serial no. 08/747,547, filed November 12, 1996;
 - d) U.S. application serial no. 08/712,710, filed September 12, 1996;
 - e) U.S. application serial no. 08/744,026, filed November 5, 1996;
 - f) U.S. application serial no. 08/786,999, filed January 23, 1997;
 - g) U.S. application serial no. 08/822,262, filed March 20, 1997; and
 - h) U.S. application serial no. 08/000,000 (as yet unassigned), filed October 16, 1997;

which applications are incorporated herein by reference and to which applications we claim priority under 35 USC '120.

In the Claims

Claims 1-32 have been canceled without prejudice.

New claims 33-36 have been added as follows: